Full Text PA-96-051

ROLE OF MICROBES IN AUTOIMMUNE AND IMMUNE-MEDIATED DISEASES

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National Institute of Allergy and Infectious Diseases
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National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Allergy and Infectious Diseases gives special consideration for funding to scientifically meritorious applications in response to Program Announcements. Program Announcements identify areas of ongoing research emphasis for the NIAID.

The National Institute of Allergy and Infectious Diseases (NIAID),
National Institute of Neurological Disorders and Stroke (NINDS) and
National Institute of Arthritis and Musculoskeletal and Skin Diseases
(NIAMS) invite applications for basic and preclinical studies to increase knowledge of the role of microbes in the development and regulation of chronic pathologic immune responses, including autoimmune diseases, and to identify the genetic factors that increase or decrease the susceptibility to pathogen-induced immune disease. Exploitation of animal models of microbe-induced autoimmune disease to molecularly dissect the etiology and pathogenesis of autoimmune disease would be relevant. The knowledge developed through research into the mechanisms by which microbes break tolerance to self antigens should provide information about the underlying basis of autoimmunity.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This program announcement (PA), Role of Microbes in Autoimmune and Immune-mediated Diseases, is related to the priority area of diabetes and chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-0325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) (R29) award.

MECHANISM OF SUPPORT

Traditional research project grant (R01), FIRST (R29), and small research grants (R03) may be submitted in response to this program announcement. The total requested project period for an application submitted in response to this PA may not exceed five years; a foreign application may not request more than three years of support.

NIAID uses R03 grants to support small highly innovative or pilot projects. Applicants for R03 grants may request up to $50,000 annual direct costs for a period not to exceed three years. Funds and time requested should be appropriate for the research proposed.
Applicants for R03 grants must follow special application guidelines,
SMALL RESEARCH GRANTS -NIAID, which appeared in the NIH Guide for Grants and Contracts, Vol. 25, No. 9, March 22, 1996, and are available from the NIAID program staff listed under INQUIRIES.

NINDS and NIAMS do not utilize the R03 mechanism.

RESEARCH OBJECTIVES

Background

Infectious agents and/or their products have been implicated in the pathogenesis of autoimmune and chronic inflammatory diseases. Reiter's syndrome and Lyme disease are chronic immune-mediated inflammatory diseases that are clearly induced by infectious agents. Infection with Campylobacter jejuni is a common antecedent of the Guillain-Barre syndrome. A workshop recently convened by the NIAID on the Role of Infectious Agents in the Development of Autoimmunity highlighted this area as important for advancing our understanding of the pathogenesis of autoimmune disease. An association of rheumatoid arthritis with various organisms, including mycoplasma, Epstein-Barr virus, parvovirus, and rubella, has been suggested, but not convincingly proven. Insulin dependent diabetes mellitus (IDDM), a metabolic disease caused by immune destruction of the pancreatic beta cells, has also been associated epidemiologically with various infectious agents, including rubella and Coxsackie virus. Recently, cross reactivity of T cell clones to both Coxsackie protein and glutamic decarboxylase (GAD65), a pancreatic islet beta cell protein and IDDM-associated antigen, has provided molecular evidence for the association of IDDM with Coxsackie virus (1-2). In addition, various viral and bacterial peptides are able to activate myelin basic protein specific T cell clones, which were isolated from patients with multiple sclerosis (3). Various mechanisms by which pathogens could induce autoimmune or immune-mediated diseases have been suggested. The organism may directly generate an immune response by its continued presence. Alternately, the organism may induce an immune response, possibly by revealing self antigens that are normally sequestered from the immune system, and this autoreactive response then becomes self-sustaining. A role for superantigens, which can be of viral or bacterial origin, has also been postulated. Superantigens are products of microbes that activate a large proportion of the host's T cells by interaction with the MHC and the variable domain of the beta-chain of their antigen receptors. Recently, isolation of islet infiltrating lymphocytes from the pancreata of two patients with newly onset IDDM provided suggestive evidence that a superantigen may be involved in the origin of this disease (4).

Many of the immune diseases associated with infection have a genetic component, suggesting that genetic susceptibility may play a role in the development of pathologic immune responses to microorganisms. In fact, the cross reactivity of T cell clones to Coxsackie protein and GAD65 was only evident in mice with a diabetes susceptible MHC background (2).

Animal models also provide evidence that infectious agents may play a role in either initiating or in protecting the host from the development of autoimmune disease. For example, the maintenance of HLA-B27 transgenic mice in germ-free conditions prevents the development of the inflammatory disease (5). However, the NOD mouse develops diabetes at an increased frequency when kept in a "clean" facility. Investigation of the role of pathogens in the development and regulation of the immune response in autoimmune or chronic immune-mediated inflammatory diseases may lead to new preventive or therapeutic strategies for these diseases.

Research Objectives and Scope

This PA is designed to support basic and preclinical research on the role of pathogens in autoimmune and immune-mediated diseases. Relevant topics of research include, but are not limited to, the following:

o mechanisms by which pathogens initiate, potentiate, or perpetuate a chronic immune response

o definition of the genetic susceptibility to chronic immunologic injury related to pathogens

o molecular, cellular, immunologic, and biological mechanisms of a host autoimmune associated response to pathogens or pathogen products

o exploitation of the known animal models of microbially-induced autoimmune disease and of the known animal models of autoimmunity for information on the role of infectious agents in their pathogenesis

o examination of whether persistence of the pathogen in the host is necessary to cause disease, or can the pathogen initiate a cascade of irreversible or reversible immunologic consequences. What factors determine the mechanism: the host, the pathogen, or both?

o hypothesis-driven investigations to establish the role of infectious agents in the etiology of various human autoimmune diseases and to determine the fraction of cases attributable to infectious agents.

The above examples of research approaches are not meant to be all inclusive or restrictive. Investigators are encouraged to develop their own innovative approaches to achieve the goals of this PA.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations), which have been in effect since 1990. The new policy contains some provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and printed in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applicants for Small Research (R03) grants are to follow the application guidelines in the NIH Guide notice entitled "SMALL RESEARCH GRANTS - NIAID".

Applicants are strongly encouraged to call program staff early in project development with any questions regarding the responsiveness of their proposed project to the goals of this PA. Applications are to be submitted on the grant application form PHS 398 (rev. 5/95) and will be accepted on the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Grants Information Office, Office of Extramural Outreach and Information, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301)435-0714, email: asknih@odrockm1.od.nih.gov.

Each application must be identified by checking "YES" on line 2 of the face page, and the number and title of this program announcement must be typed in section 2. The completed original and five legible, single-sided copies of the application must be sent or delivered to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817-7710 (for express/courier service)

R03 APPLICANTS ONLY: Direct inquiries regarding review issues and special instructions for application preparation and mail two copies of the R03 application and all five sets of any appendices to:

Stanley Oakes, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4C06
6003 Executive Boulevard
Bethesda, MD 20892-7610
Telephone: (301) 496-7042
FAX: (301) 402-2638
Email: stanley_oaks@nih.gov

FIRST (R29) applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

REVIEW CONSIDERATIONS

Applicants for all Small Research (R03) grants must see the REVIEW CONSIDERATIONS section of the notice "SMALL RESEARCH GRANTS - NIAID."

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be reviewed for scientific and technical merit in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally about 50 percent of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

o scientific, technical, or medical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research;

o adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research.

The initial review group will also examine the provisions for the protection of human and animal subjects and the safety of the research environment. Concerns expressed by the initial review group about any of these factors may influence the recommendation of the National Advisory Allergy and Infectious Diseases Council or the advisory council for NIAMS or NINDS.

AWARD CRITERIA

The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance among research areas of the program announcement, availability of funds.

INQUIRIES

Written and telephone inquiries concerning this PA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Elaine Collier, M.D.
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A. P. Kerza-Kwiatecki, Ph. D.
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Susana Serrate-Sztein, M.D.
Arthritis Branch
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Email: szteins@ep.niams.nih.gov

Direct inquiries regarding fiscal matters to:

Mrs. Pamela Fleming
Division of Extramural Activities

National Institute of Allergy and Infectious Diseases
Solar Building, Room 4B30
Executive Boulevard - MSC 7610
Bethesda, MD 20892-7610
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Ms. Carol Fitzpatrick
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AUTHORITY AND REGULATIONS

The program is described in the Catalog of Federal Domestic Assistance, No. 93.855 - Immunology, Allergy and Transplantation Research, No. 93.853 - Clinical Research of Neurological Disorders and Stroke, and No 93.846 - Arthritis, Musculoskeletal and Skin Diseases Research. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Return to PA Index

Return to NIH Guide Main Index